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Pseudoneglect is maintained in aging but not in mild Alzheimer's disease: new insights from an enumeration task

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ABSTRACT

Neurologically healthy young adults display a behavioral bias, called pseudoneglect, which favors the processing of stimuli appearing in the left visual field. Pseudoneglect arises from the right hemisphere dominance for visuospatial attention. Previous studies investigating the effects of normal aging on pseudoneglect in line bisection and greyscale tasks have produced divergent results. In addition, scarce systematic investigations of visual biases in dementia have been reported. The aim of the present study was to evaluate whether the leftward bias appearing during an enumeration task in young adults would be preserved in normal aging and at different stages of severity of Alzheimer's disease. In Experiment 1, young and older healthy adults showed a comparable pseudoneglect, performing better when targets appeared in the left visual field. In Experiment 2, the leftward bias was maintained in amnesic mild cognitive impairment patients (aMCI), but it vanished in mild Alzheimer's disease patients (AD). The maintenance of pseudoneglect in normal aging and in aMCI patients is consistent with compensatory phenomena involving the right fronto-parietal network, which allow maintaining the right hemisphere dominance. Conversely, the lack of pseudoneglect in the sample of AD patients likely results from a loss of the right hemisphere dominance, caused by the selective degeneration of the right fronto-parietal network. These results highlight the need of further systematic investigations of visuospatial biases along the continuum of normal and pathological aging, both for a better understanding of the changes characterizing cognitive aging and for improvements in the evaluation of neglect in Alzheimer's disease.

1. Introduction

Pseudoneglect refers to a behavioral bias observable in neurologically healthy individuals favoring the processing of stimuli appearing in the left hemifield (Bowers and Heilman, 1980; Brooks et al., 2014; Jewell and McCourt, 2000; Sosa et al., 2010). Pseudoneglect has been typically assessed with the same tasks used to examine neglect in clinical populations, such as line and shape bisection tasks, cancellation and greyscales tasks (Bowers and Heilman, 1980; Bradshaw et al., 1986; Jewell and McCourt, 2000; Mattingley et al., 1994; Vingiano, 1991). In addition, leftward biases have been observed in the processing of a variety of visuospatial stimuli (e.g., faces, shapes, arrays of dots or stars) presented both under tachistoscopic and free-viewing conditions (Voyer et al., 2012). Several studies provided evidence that healthy participants tend to base their judgments concerning emotional valence, brightness, size or numerosity on the leftward features of the stimuli (Campbell, 1978; Heller and Levy, 1981; Luh et al., 1991; Mattingley et al., 1994; Milner and Dunne, 1977; Nicholls et al., 1999). Recent studies have found evidence of pseudoneglect also in visual search tasks (Nicholls et al., 2014, 2017). These behavioral biases are deemed to reflect a different gradient of perceptual efficiency along the visual field, arising from a right hemisphere dominance for visuospatial attention processing (Corbetta and Shulman, 2002; Heilman and Van Den Abell, 1980; Kinsbourne, 1993; Mesulam, 1981; Reuter-Lorenz et al., 1990). Several neuroimaging and clinical data consistently support the existence of a higher-order asymmetry in the control of spatial attention (e.g., Cai et al., 2013; Çiçek et al., 2009; Fink et al., 2000; Foxe et al., 2003; Halligan et al., 2003).

How pseudoneglect and the underlying mechanisms change with aging is still a debated issue: while some studies reported a reduction and even a directional reversal of pseudoneglect in older healthy adults (Barrett and Craver-Lemley, 2008; Benwell et al., 2014b; Failla et al., 2003; Fujii et al., 1995; Schmitz and Peigneux, 2011), other studies reported no effect of aging on leftward bias or even a stronger leftward bias with age (Brooks et al., 2016; De Agostini et al., 1999; Friedrich et al., 2016; Varnava and Halligan, 2007). Two models of cognitive aging have mainly been used to account for age-related changes in spatial asymmetry: the hemispheric asymmetry reduction in older

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adults (HAROLD) and the right hemi-aging model (RHAM). HAROLD model postulates that cognitive functions are highly lateralized in one hemisphere in young adults but they become progressively less lateralized with aging (Cabeza, 2002; Sander and Cabeza, 2005). RHAM model claims that the right hemisphere, and consequently the cognitive functions mainly sustained by this hemisphere, are more sensitive to age-related decline and thus show a more pronounced deterioration (Albert and Moss, 1988; Goldstein and Shelly, 1981). Ultimately, both models ascribe the lack of leftward bias in aging to a reduction of hemispheric imbalance between the right and the left hemisphere activations. On the contrary, the "compensation-related utilization of neural circuits hypothesis" (CRUNCH; Reuter-Lorenz and Campbell, 2008), a model of cognitive aging complementary to HAROLD model, has been used to account for the maintenance of leftward bias in normal aging (Friedrich et al., 2016). CRUNCH predicts that older adults recruit additional brain areas in comparison to younger adults, according to the task demands. When the additional areas are located in the right hemisphere, the hemispheric imbalance is maintained and accordingly also the leftward spatial bias. Investigating whether and how aging affects perception across the two hemifields is important not only for the comprehension of pseudoneglect phenomenon but also to enrich knowledge on the mechanisms of cognitive aging (Brooks et al., 2014). Additionally, extending the investigation through pathological aging will provide interesting hints for the understanding of how attentional lateralization changes when physiological aging breaks down, targeting possible interventions.

In the present study, we aimed to evaluate the presence of pseudoneglect in normal young and older adults during an enumeration task and to investigate whether pseudoneglect was modulated by pathological aging. The enumeration task allowed us to evaluate whether the leftward bias could be generalized to paradigms that are not typically used to study pseudoneglect. In addition, since enumeration more likely requires higher attentional resources than line bisection tests, it may be useful to investigate whether pseudoneglect is found irrespective of attentional demands.

We tested amnesic mild cognitive impairment (aMCI) and mild Alzheimer's disease (AD) patients, which represent different progressive phases of the most frequent cause of age-related dementia (i.e. Alzheimer's disease). Despite the fact that it is now largely recognized that attentional and visuospatial deficits often accompany memory impairment even in the earliest stages of AD (for a review see Finke et al., 2013), the investigation of unilateral neglect or spatial lateralization biases in AD has been commonly overlooked, with a focus on other cognitive domains (e.g. memory, language).

The data used in the present study were originally collected in our laboratories and partially used for two studies aimed at investigating the age-related neural changes in attention and working memory during enumeration (Bagattini et al., 2017; Pagano et al., 2015).

2. Material and methods

2.1. Participants

Eighteen right-handed young adults (16 females, mean age = 23.3, SD = 3.7, range = 18–32) and 26 right-handed older adults (14 females, mean age = 70.5, SD = 4.3, range = 65–80) participated in Experiment 1. Twenty-three right-handed healthy older controls (HC; 15 females, mean age = 69.5, SD = 4.1, range = 64–82), 20 right-handed aMCI patients (10 females, mean age = 75.7, SD = 5.9, range = 60–83) and 21 right-handed mild AD patients (12 females, mean age = 75.6, SD = 6.5, range = 63–85) were recruited in Experiment 2. Experiment 1 and experiment 2 included respectively all the participants to Pagano et al. (2015) and to Bagattini et al. (2017), and some more participants who were previously been rejected due to excessive noise or technical problems in EEG recording.

Inclusion criteria for aMCI patients were a Mini-Mental State Examination (MMSE) score ≥ 24 and a Clinical Dementia Rating scale (CDR) score = .5 (Petersen, 2004), while for AD patients they were a diagnosis of probable AD according to Mckhann et al. (1984), a MMSE score ≥ 20, a CDR score ≤ 2 and a stable dose of cholinesterase inhibitors for at least 3 months prior to participation in the study. Exclusion criteria were the presence of medical, neurological or psychiatric disorders that might interfere with the study. All participants reported normal or corrected-to-normal sight, as well as normal color vision. In order to assess cognitive functioning, older participants underwent a detailed neuropsychological evaluation, testing general cognitive abilities (MMSE), memory (Rey Auditory Verbal Learning test immediate and delayed recall; digit span; recall of Rey-Osterrieth Complex figure) attention and visuo-spatial abilities (Attentive matrices; Trail Making test part A and B; Stroop test), language (verbal fluency), non-verbal reasoning (Raven's Colored Progressive Matrices) and praxia (Copy of Rey-Osterrieth Complex figure). Results of the neuropsychological tests are summarized in Table 1.

Table 1
Demographic and neuropsychological data relative to the groups of older participants recruited in Experiment 1 (Older) and Experiment 2 (HC, aMCI and AD). The table represents age- and education-adjusted values for each test, reported as mean (± SD).

	Experiment 1	Experiment 2		
	Older	HC	aMCI	AD
Age (years)	70.5 (4.3)	69.4 (4.1)	75.1 (6.0)	76.4 (6.6)
Education (years)	12.0 (2.7)	10.4 (4.0)	8.3 (2.9)	7.7 (2.7)
MMSE	26.4 (1.1)	27.7 (2.0)	26.2 (1.6)	22.2 (1.4)
RCPM 47	35 (3)	32.3 (3.3)	30.0 (4.5)	26.4 (5.9)
RAVLT-immediate recall	51.9 (8.9)	44.5 (8.3)	36.4 (8.2)	28.1 (6.2)
RAVLT-delayed recall	12.8 (2.3)	10.3 (1.9)	6.5 (3.1)	3.1 (1.7)
ROCF-copy	35.6 (1.4)	35.7 (1.5)	32.8 (5.6)	26.3 (9.0)
ROCF-recall	20.2 (5.1)	18.3 (4.5)	12.3 (6.7)	7.8 (3.3)
Digit Span	5.6 (.8)	5.6 (.9)	5.7 (.8)	5.6 (1.0)
Verbal fluency	38.9 (9.1)	38.4 (9.5)	28.4 (8.0)	27.9 (8.0)
Attentive matrices	53.7(4.3)	46.0 (6.2)	43.0 (8.7)	36.0 (12.4)
TMT A	22.8 (10.3)	27.4 (11.4)	51.4 (35.3)	75.5 (59.2)
TMT B	72.0 (42.4)	71.8 (38.5)	107.1 (66.5)	141.4 (46.7)
Stroop-reaction times	21.0 (15.9)	15.8 (6.9)	29.7 (20.5)	45.6 (28.2)
Stroop-errors	.2 (1.9)	.2 (.8)	1.9 (2.7)	3.5 (6.1)

Abbreviations: Mini Mental State Examination-MMSE, Raven Progressive Colored Matrices-RCPM 47; Rey Auditory Verbal Learning Test-RAVLT, copy and recall of Rey-Osterrieth complex figure-ROCF, Digit span forward, Verbal fluency with phonemic cue, Attentive matrices, Trail Making Test-TMT A and B, Stroop Test.

All participants gave their written informed consent prior to the beginning of the experiment. All the procedures conformed to the Declaration of Helsinki for research involving human subjects and were approved by the ethics committee of University of Trento and by the ethics committee of the IRCCS San Giovanni di Dio Fatebenefratelli Scientific Institute of Brescia.

2.2. Stimuli and procedure

The same visual enumeration task was used in Experiment 1 and Experiment 2. Participants were required to enumerate a variable number (from 1 to 6) of uniquely colored targets (either red or green) presented in the right or left visual field together with distractors (either green or red). Stimuli consisted of 24 equiluminant red and green dots (.97°, 35 cd/m^2) presented on a dark grey background (22 cd/m^2) and equally distributed in the two visual fields. The dots were displayed within an invisible grid of 8 rows × 10 columns (13.8° × 16.4°) centered on the fixation. Targets never appeared in the extreme columns and rows of the matrix, or in the columns adjacent to the fixation. Each trial began with a fixation dot, followed by the stimulus configuration, which was displayed for 600 ms in Experiment 1 and for 400 ms in

Experiment 2. Participants' task was to report the number of targets. In Experiment 1, participants provided their response using the computer mouse, by clicking one out of six squares presented on the screen. In Experiment 2, the response was reported verbally and acquired by the experimenter through the keyboard. Only participants in Experiment 1 were required to keep their eyes on the fixation point, while participants in Experiment 2 were simply instructed to bring their gaze back on the central fixation dot at the beginning of each trial. Because the experiments were carried out with the main purpose of investigating event-related potentials during the enumeration task (Bagattini et al., 2017; Pagano et al., 2015), participants were required to complete a high number of trials. A total of 960 trials (16 blocks, 160 trials for each level of numerosity) were delivered in Experiment 1, while, considering the lower attentional resources of AD patients, a total of 600 trials were delivered in Experiment 2 (10 blocks, 100 trials for each level of numerosity). Nevertheless, only 15 HC (out of 23), 9 aMCI (out of 20) and 13 AD (out of 21) completed the entire experiment, which lasted about 90 min, including the electroencephalographic cap montage. Most of the other participants completed from 6 to 8 blocks, except 1 aMCI and 1 AD patients, who completed 4 and 5 blocks respectively. Participants were allowed short rest breaks after each block.

2.3. Statistical analyses

All statistical analyses were performed on the mean error rate, which was arcsine-transformed due to a violation of normal distribution (Snedecor and Cochran, 1967). Data of Experiment 1, as well as data of Experiment 2, were submitted to a mixed-model ANOVA, with *group* (younger vs. older in Exp. 1; HC vs. aMCI vs. AD in Exp. 2) as between-subjects factor, *visual field* (left vs. right) and *numerosity* $(1-6)$ as within-subjects factors. When appropriate, the Greenhouse-Geisser epsilon correction factor was applied to compensate for non-sphericity in the measurements. Post-hoc comparisons were performed with Sidak correction for multiple comparisons. In line with the leftward perceptual bias associated with pseudoneglect (Brooks et al., 2014; Jewell and McCourt, 2000), lower error rates in the left visual field were considered as evidence of pseudoneglect.

Accuracy lateralization indexes were also calculated, as the difference in accuracy (%) between the right and the left visual field divided by the sum of accuracy (%) of the right and the left visual field. Accordingly, positive indexes values indicated a rightward bias, whereas negative values indicated a leftward bias. These indexes were used only for graphical depictions (see Figs. 1 and 2), they were not submitted to separate statistical analyses.

3. Results

Results of the analysis performed on Experiment 1 (Fig. 1) showed a consistent main effect of *visual field* [$F(1,42) = 6.43$, $\eta_p^2 = .133$, $p = .015$], which denoted a lower error rate in the left than in the right visual field. The pseudoneglect effect was evident in both younger and older adults, as revealed by the lack of significant interaction between *visual field* and *group* [$F(1,42) = .05$, $\eta_p^2 = .001$, $p = .83$], and principally involved numerosities 3 and 4, as indicated by the marginal interaction between *visual field* and *numerosity* [$F(5,210) = 2.36$, $\eta_p^2 = .053$, $p = .079$]. The main effect of *numerosity* [$F(5,210) = 81.79$, $\eta_p^2 = .661$, $p < .001$] indicated an overall increase in error rates as a function of target numerosity, and a trend toward significance of the factor *group* [$F(1,42) = 3.04$, $\eta_p^2 = .067$, $p = .089$] showed that older adults tended to perform worse than younger adults. Consistently with results reported in Pagano et al. (2015), older participants showed a general reduction of the ability to enumerate targets, which was not affected by target numerosity nor by visual field presentation (*group* × *numerosity* [$F(5,210) = 2.19$, $\eta_p^2 = .050$, $p = .11$]; *group* × *visual field* × *numerosity* [$F(5,210) = .28$, $\eta_p^2 = .007$, $p = .82$]).

The ANOVA performed on the data of Experiment 2 (Fig. 2) indicated a significant effect of the main factor *visual field* [$F(1,61) = 9.67$, $\eta_p^2 = .137$, $p = .003$], which also interacted with *group* [$F(2,61) = 6.09$, $\eta_p^2 = .167$, $p = .004$]. Post-hoc comparisons revealed a difference between the two visual fields (with lower error rates in the left than in the right visual field) in HC ($p < .001$) and in aMCI patients ($p = .008$), but not in AD patients ($p = .32$). The factor *visual field* interacted also with *numerosity* [$F(5,305) = 6.10$, $\eta_p^2 = .091$, $p = .001$], suggesting that the pseudoneglect effect was significant only at the highest numerosities ($p = .001$ at numerosity 5; $p = .005$ at numerosity 6). This effect, however, cannot be more precisely described across the groups, because the interaction *visual field X group* X *numerosity* did not reach significance [$F(10,305) = 1.32$, $\eta_p^2 = .042$, $p = .25$]. The analyses revealed also main effects of *group* [$F(2,61) = 17.49$, $\eta_p^2 = .364$, $p < .001$], *numerosity* [$F(5,305) = 134.48$, $\eta_p^2 = .688$, $p < .001$] and their interaction [*group* X *numerosity* $F(10,305) = 8.13$, $\eta_p^2 = .211$, $p < .001$], confirming that the group of AD patients performed worse than both the groups of HC and aMCI patients for all target numerosities (all $p < .031$), except for numerosity 3 in comparison to aMCI patients ($p = .31$). No difference arose between HC and aMCI patients' performance (all $p > .22$).

Results of Experiment 2 were replicated when data were submitted to an ANCOVA with *age* as covariate to account that groups were not matched for age ($p \leq .001$), further supporting that age per se does not impact lateralization indexes, as revealed in Experiment 1.

4. Discussion

The present study aimed at extending the knowledge on pseudoneglect in young adults to healthy older adults and to patients with different stages of severity of Alzheimer's disease. Previous studies exploring the effect of normal aging on pseudoneglect produced divergent results (Barrett and Craver-Lemley, 2008; Benwell et al., 2014b; Brooks et al., 2016; De Agostini et al., 1999; Failla et al., 2003; Friedrich et al., 2016; Jewell and McCourt, 2000; Schmitz and Peigneux, 2011; Varnava and Halligan, 2007), while scarce systematic investigations of visual biases in dementia have been reported (Bartolomeo et al., 1998; Foster et al., 1999; Ishiai et al., 2000, 1996; Mendez et al., 1997; Venneri et al., 1998). Our data indicate that both young and older healthy adults performed better an enumeration task when targets appeared in the left than in the right visual field. This leftward bias was maintained in the prodromal stage of Alzheimer's disease (i.e., aMCI), while it vanished when the dementia progressed to the early stage. Mild AD patients, indeed, showed no difference in the performance between the two visual fields.

There is agreement in literature on the right hemisphere dominance for the processing of visuospatial information (De Renzi, 1982; Gazzaniga, 2000; Milner and Dunne, 1977; Nebes, 1974). Consistently, in young adults, behavioral asymmetries favoring the left visual field were reported in several visuospatial tasks (Campbell, 1978; Heller and Levy, 1981; Jewell and McCourt, 2000; Luh et al., 1991; Mattingley et al., 1994; Nicholls et al., 1999, 2017). A right hemisphere specialization has been suggested also for the subitizing component of enumeration, which is the fast and accurate labeling of small quantities of simultaneously presented items (Jackson and Coney, 2004; Kimura and Durnford, 1974; Pasini and Tessari, 2001; Warrington and James, 1967; but see Butterworth, 1999). It has been claimed, however, that the left bias found in enumeration tasks concerns the visuospatial processing required for the task more than enumeration abilities per se (Boles, 1986; Kimura, 1966). Left visual field superiority, indeed, was found in numerosity-related tasks when participants were required to enumerate simple nonverbal stimuli (Boles, 1986; Kimura, 1966; Pasini and Tessari, 2001), but also when they had to judge numerosity without counting (Luh et al., 1991; Nicholls et al., 1999). On the contrary, it was not found when the enumeration task involved verbal material or required verbalization (Boles, 1986; Kimura, 1966; Pasini and Tessari, 2001). Accumulating evidence coming from several studies (e.g., Mazza

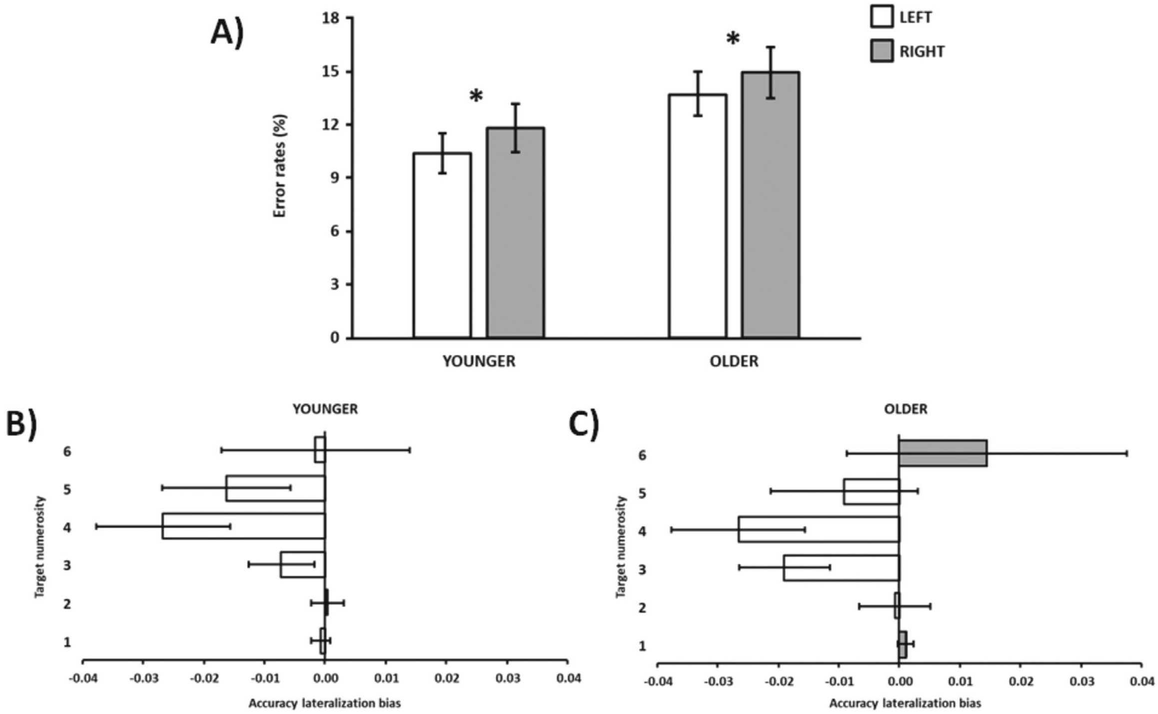

Fig. 1. Enumeration performance in younger and older adults (Experiment 1). (A) Mean error rates (%) as a function of left (white bar) and right (grey bar) visual field in younger and older adults. **(B-C)** Mean accuracy lateralization indexes towards the left (white bars) and the right (grey bars) visual field as a function of target numerosities in younger **(B)** and older adults **(C)**. The accuracy lateralization indexes were calculated as the difference in accuracy (%) between the right and the left visual field divided by the sum of accuracy (%) of the right and the left visual field. Positive values indicate a rightward bias, whereas negative values indicate a leftward bias. Error bars represent the standard error of the mean (± SEM). Asterisks depict significant differences.

and Caramazza, 2011; Mazza et al., 2013; Pagano et al., 2016; Ansari et al., 2007; Vetter et al., 2008, 2011) converges on explaining subitizing as an attention-ground phenomenon, thus giving to attention a key role in the enumeration process. In the present study, we found a general left visual field superiority in a dot enumeration task in young normal adults, thus we speculate that the nature of this lateralization is the same as the one found in line bisection tasks. Compared to these tasks, enumeration likely requires more attentional resources, and for this reason the leftward bias may be more consistent.

Crucially to the aim of the present study, we found a consistent pseudoneglect also in healthy older participants. While pseudoneglect was previously demonstrated in some studies on older adults in line bisection and greyscale tasks (Brooks et al., 2016; De Agostini et al., 1999; Friedrich et al., 2016; Varnava and Halligan, 2007), this is the first demonstration in enumeration tasks of the existence of this perceptual bias through aging.

The presence of pseudoneglect in older adults in both Experiment 1 and Experiment 2, which differed in some methodological details, strengthens the reliability of the results. Our data further lend support to the idea that pseudoneglect can exist in the absence of overt eye movements (Nicholls et al., 2017) and that it is not an oculomotor bias (Nuthmann and Matthias, 2014). In Experiment 2, participants were not constrained to maintain central fixation during target presentation. Thus, although the brief exposure duration (i.e., 400 ms) should have discouraged the tendency for eye movements, we cannot exclude that the first saccades were biased toward the left visual field (Dickinson and Intraub, 2009; Foulsham et al., 2013). In Experiment 1 participants were instructed to avoid any saccade and the same leftward advantage for dot enumeration was still found. We have to acknowledge, however, that, although the compliance with instructions was high in Experiment 1, a strict check of eye-movement would have been necessary to guarantee the absence of eye-movements.

Some evidence showed that the hand used in the task may affect the leftward perceptual asymmetry (Brodie and Pettigrew, 1996; MacLeod and Turnbull, 1999; McCourt et al., 2001; Roig and Cicero, 1994; Schiff and Truchon, 1993; but see Jewell and McCourt, 2000; Nicholls et al., 2001; Nicholls and Roberts, 2002). For instance, Failla and colleagues (2003) found that pseudoneglect was comparable in older and younger participants only when they used the left hand, while a reduction due to aging was measured when they used the right hand. In the present study it is noteworthy that a leftward bias equally arose in older adults with two different response modalities, both requiring the primary involvement of the left hemisphere: a right unimanual response in Experiment 1 and a verbal response in Experiment 2.

As mentioned in the Introduction, the results on pseudoneglect and aging are thus far contradictory. Indeed, the present results are at odds with some previous studies reporting an attenuation or a reversal of pseudoneglect in normal aging (Barrett and Craver-Lemley, 2008; Benwell et al., 2014b; Fujii et al., 1995; Learmonth et al., 2017; Schmitz and Peigneux, 2011). These studies have explained the age-related changes in spatial asymmetry within the frame of the HAROLD (Cabeza, 2002; Sander and Cabeza, 2005) and RHAM models of cognitive ageing (Albert and Moss, 1988; Goldstein and Shelly, 1981), which argue for a more balanced activation of the two hemispheres in older age. The results of the present study, which reported the maintenance of pseudoneglect in older adults, did not confirm the expectations predicted by these influential models of cognitive aging. Nevertheless, HAROLD model was not specifically conceived to take into account the visuospatial domain. The bilateral recruitment postulated by HAROLD model, indeed, was specific for tasks requiring a main involvement of the prefrontal cortex, such as episodic memory encoding and retrieval, semantic memory retrieval, working memory and inhibitory control (Cabeza, 2002; Sander and Cabeza, 2005). Thus, it may not be generalizable to age-related changes in an enumeration task (Brooks et al., 2014; Friedrich et al., 2016; Learmonth et al., 2017), which mainly activates temporo-parietal areas (Ansari et al., 2007; Vetter et al., 2011; Vuokko et al., 2013). Evidence supporting RHAM model comes from studies in the areas of verbal/spatial, affective, and sensorimotor

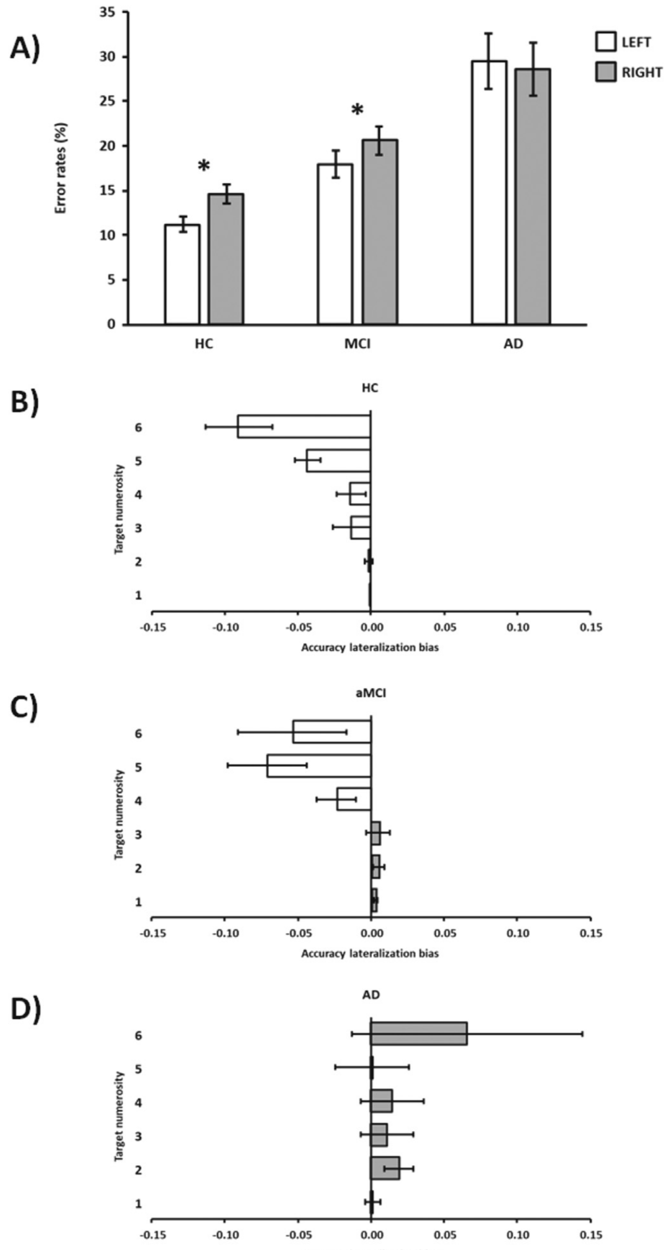

Fig. 2. Enumeration performance in HC, aMCI and AD patients (Experiment 2). (A) Mean error rates (%) as a function of left (white bar) and right (grey bar) visual field in HC, aMCI and AD patients. **(B-D)** Mean accuracy lateralization biases towards the left (white bars) and the right (grey bars) visual field as a function of target numerosities in HC **(B)**, aMCI patients **(C)** and AD patients **(D)**. The accuracy lateralization indexes were calculated as in Fig. 1. Error bars represent the standard error of the mean (± SEM). Asterisks depict significant differences.

functions, but they lead to divergent results, providing inconclusive proofs (Dolcos et al., 2002; Gerhardstein et al., 1998; Nebes, 1990). The maintenance of pseudoneglect in our sample of older adults is in line with the CRUNCH model, which predicts that processing inefficiencies cause the aging brain to recruit more neural resources to achieve a computational output equivalent to that of a younger brain. At lower levels of task demand, overactivation in older adults is associated with good performance and presumably is compensatory because performance differences are minimal despite activation differences. For harder tasks, a resource ceiling is reached, leading to age-related behavioral decrements (Reuter-Lorenz and Campbell, 2008). Overactivation has been found for a broad range of tasks, across a variety of brain regions, and, interestingly, it did not necessarily concern contralateral areas, as predicted in HAROLD model, but also the same cortical sites or networks recruited in the young. This latter possibility would leave unaltered the imbalance between the two hemispheres, justifying the maintenance of leftward bias with aging (Learmonth et al., 2017). Accordingly, we have recently reported electrophysiological evidence supporting CRUNCH model in older adults performing an enumeration task (Pagano et al., 2016). We found a neural overactivation associated with good levels of performance in an easy task condition, but no overactivation (and a decline in performance) during the more demanding task condition.

Although pseudoneglect has long been considered as a consequence of a right hemisphere dominance for visuospatial attention, the neural structures underlying this phenomenon have rarely been investigated. To this regard, a crucial step forward is represented by the brilliant study of Thiebaut de Schotten et al. (2011), who reported the first evidence that the right hemisphere dominance for visuospatial attention is caused by a larger fronto-parietal network in the right than in the left hemisphere. Specifically, the three white matter tracts of the superior longitudinal fasciculus (SLF) that compose the fronto-parietal connections show a dorsal to ventral gradient of lateralization, with the dorsal branch being symmetrically distributed between the two hemispheres and the ventral branch being anatomically larger and strongly lateralized in the right hemisphere (Thiebaut de Schotten et al., 2011). Interestingly, the lateralization of the middle branch correlated with the behavioral signs of right hemisphere dominance, such that a larger leftward bias in behavior was associated with a larger volume of the white matter tract in the right hemisphere (Thiebaut de Schotten et al., 2011). Converging evidence from electroencephalographic studies (Benwell et al., 2014a; Foxe et al., 2003) identified an early lateralized ERP correlate of spatial bias, that was source localized in the right ventral attention network (i.e., temporo-parietal junction), a region strongly involved also in enumeration (Ansari et al., 2007). Importantly, this ERP response was found to correlate with the associated behavioral spatial bias across participants (Benwell et al., 2014a). Regarding the physiological modulations of the fronto-parietal network during aging, a very recent fMRI study (Deslauriers et al., 2017) reported that older adults exhibited an increased connectivity along the fronto-parietal connections within the ventral attention network (Corbetta and Shulman, 2002; Fox et al., 2006), which likely corresponds to the right lateralized ventral branch of SLF. Furthermore, the middle branch of SLF was reported to be functionally intact in older adults (Kurth et al., 2016). Accordingly, the maintenance of pseudoneglect in our sample of older adults may be explained by the fact that, despite the age-related reduction of neural resources, the right fronto-parietal network might still maintain its predominance, thus inducing the behavioral leftward bias. This interpretation is only speculative, and further neuroimaging studies are necessary to clarify the neural mechanisms subtending the maintenance of pseudoneglect in healthy aging.

The second aim of the study was to investigate pseudoneglect in pathological aging. To our knowledge, this is the first study that investigated perceptual biases in an enumeration task along the continuum of AD severity. Our results showed that pseudoneglect was maintained in aMCI, but it disappeared when the disease severity advanced to mild AD. There is growing evidence from neuropathological, electrophysiological and neuroimaging studies that Alzheimer's disease may be considered as a disconnection syndrome (for a review see Delbeuck et al., 2003). AD degeneration specifically affects brain regions involved in cortico-cortical connections, and particularly those between anterior and posterior areas (Delbeuck et al., 2003). Consistently, several electrophysiological and imaging studies reported a reduction of fronto-parietal connectivity in AD patients (Berendse et al., 2000; Horwitz et al., 1986; Neufang et al., 2011; Zhang et al., 2015). We can thus speculate that the different pattern of perceptual biases observed in aMCI and AD patients may depend on the different levels of selective degeneration of the fronto-parietal network that characterize the progression of the disease. While in mild AD patients the lack of pseudoneglect is consistent with the loss of the right hemisphere dominance- caused by the selective degeneration of the right-lateralized fronto-parietal ventral connections- in aMCI patients the maintenance of pseudoneglect may be supported by compensatory mechanisms (Scheller et al., 2014; Zhang et al., 2015). Interestingly, by investigating spontaneous functional connectivity of the fronto-parietal network in pathological aging, Zhang and colleagues (Zhang et al., 2015) observed a differential pattern of degeneration for aMCI and AD in dorsal and ventral pathways. Whereas within the dorsal component the connectivity impairment enhanced along disease severity progression, ventral right-lateralized connectivity was decreased in AD patients but enhanced in aMCI patients. Accordingly, by recording EEG activity during the execution of the same enumeration task here used (Bagattini et al., 2017), we have demonstrated a compensatory neural over-activation in aMCI patients but not in AD patients. The hyperactivation of the brain areas involved in the execution of the task may allow aMCI patients to overcome the early neural decline maintaining a good level of performance. Thus, the supposed compensatory hyperactivation of the right fronto-parietal network may induce the maintenance of the right hemisphere dominance and, thus, the maintenance of the leftward lateralization bias in aMCI patients.

An actual evidence against this reasoning is that AD pathology is not a focal disease, but it is usually characterized by bilateral neurodegeneration, and consequently the dominance relation across the two hemispheres should be maintained independently of the cortical degeneration. Several indications, however, have been provided that AD pathology may show an asymmetric pattern of brain atrophy (Braak et al., 1993; Derflinger et al., 2011; Finke et al., 2013; Haxby et al., 1985). Some studies also reported that signs of unilateral spatial neglect in AD patients correlated with more severe cortical atrophy in the contralateral hemisphere (Bartolomeo et al., 1998; Ishiai et al., 2000; Redel et al., 2012; Sorg et al., 2012; Venneri et al., 1998). From this point of view, modulations of the normal pattern of pseudoneglect could be expected in AD patients to be subjected to a high inter-individual variability, rather than to be a peculiar specificity of the disease. Accordingly, lateralization biases in AD patients have been reported to occur both in favour of the right (Ishiai et al., 2000, 1996; Mendez et al., 1997; Venneri et al., 1998) and of the left visual field (Bartolomeo et al., 1998; Foster et al., 1999). Nevertheless, comparisons between AD patients and healthy controls have rarely been performed. In the present study, despite the fact that the effect was not statistically significant, AD patients displayed a visual trend opposite to that observed in healthy elderly and in aMCI patients: they apparently performed better when targets appeared in the right than in the left visual field. Considering that the AD patients recruited in this study had a diagnosis of mild AD, while most of the studies reporting a rightward bias was conducted on AD patients in later stages of disease severity (Ishiai et al., 2000, 1996; Mendez et al., 1997; Venneri et al., 1998), we can speculate that the spatial bias may gradually worsen with AD severity progression.

A limitation of the present study is the absence of a precise assessment of the participants' eyesight. Visual deficits were assessed during the medical history investigation using self-report, and the main ones represented exclusion criteria for the participation in the study. We cannot exclude, however, slight differences in low level visual abilities across the groups of participants, which could affect results.

In conclusion, the present study provides a comprehensive picture of the visuospatial behavioral bias emerging during an enumeration task along normal and pathological aging. While the pseudoneglect observed in young adults was maintained in older healthy adults and in aMCI patients, the behavioral difference across the two visual fields disappeared in AD patients. This evidence of pseudoneglect in normal aging and in aMCI patients is consistent with compensatory phenomena involving the right fronto-parietal network, which are no longer effective in AD patients. Further systematic investigations are necessary to corroborate these findings on visuospatial biases along the continuum of normal and pathological aging.

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Conflicts of interest

None.

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